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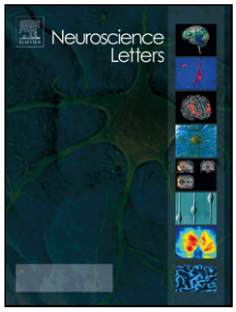

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Why do so many genetic insults lead to Purkinje Cell degeneration and spinocerebellar ataxia?

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Highlights

- Purkinje Cell specific genes highlight pathways converging onto calcium signaling
- Calcium signaling contributes to Purkinje cell vulnerability for SCA mutations
- Unique Purkinje Cell genes might be candidate - or modifier genes of SCA disease

Abstract

The genetically heterozygous spinocerebellar ataxias are all characterized by cerebellar atrophy and pervasive Purkinje Cell degeneration. Up to date, more than 35 functionally diverse spinocerebellar ataxia genes have been identified. The main question that remains yet unsolved is why do some many genetic insults lead to Purkinje Cell degeneration and spinocerebellar ataxia? To address this question it is important to identify intrinsic pathways important for Purkinje Cell function and survival. In this review, we discuss the current consensus on shared mechanisms underlying the pervasive Purkinje Cell loss in spinocerebellar ataxia. Additionally, using recently published cell type specific expression data, we identified several Purkinje Cell-specific genes and discuss how the corresponding

pathways might underlie the vulnerability of Purkinje Cells in response to the diverse genetic insults causing spinocerebellar ataxia.

Keywords: Purkinje Cell; spinocerebellar ataxia; genetic mechanisms; neurodegeneration; pathway analysis.

Introduction

Autosomal dominant cerebellar ataxias (ADCAs) are a group of hereditary neurodegenerative disorders caused by pervasive Purkinje Cell (PC) loss in the cerebellum. These disorders are also referred to as spinocerebellar ataxias (SCA) by genetic nomenclature [1]. For now, 49 subtypes of SCA for which 37 causative genes are identified (Table 1). The genetically diverse SCA type are relatively homogeneous in their clinical presentation as they are all characterized by cerebellar ataxia, but can also be accompanied by additional signs and symptoms [1,2]. In general, patients experience problems with their coordination and balance, poor hand-eye coordination, dysarthria, and involuntary eye movements.

Genetically, SCA can be classified into the following two categories: 1) non-conventional SCA types and 2) conventional SCA types. The first group of SCAs is caused by expansions of coding CAG repeats encoding long stretches of polyglutamine (polyQ) and include SCA1-3, 6, 7, and 17, or by non-coding repeat expansions in either untranslated regions (UTRs) or intronic regions including SCA8 (CTG or CAG repeats depending on the direction of transcription), SCA10 (ATTCT repeats), SCA12 (CAG repeats), SCA31 (TGGAA repeats), and SCA36 (GGCCTG repeats), and SCA37 (ATTTC repeat) [1,3,4]. In recent years the second group of SCAs is growing as more SCAs due by conventional mutation are found by next generation sequencing. This group includes missense mutations, as for in example SCA5, 13, 14, 19/22, and 23, and large duplications or deletions of single genes or gene regions that cause SCA15/16, SCA20, and SCA39 [1,5-8]. These different mutations in functionally diverse SCA genes all lead to pervasive PC loss, however the molecular mechanisms to this common pathology are not yet known.

Recent scientific advances have begun to shed light on the shared pathogenesis of the genetically heterogeneous SCAs. To elucidate the shared route to pervasive PC degeneration, researchers often used the reported SCA genes as staring point [9-12]. This has led to the identification of several potential mechanisms underlying SCA. These mechanisms include, but are not limited to, protein misfolding and aggregation, toxic RNA gain-of-function, transcriptional dysregulation, and alterations in glutamate and calcium signaling affecting synaptic transmission. The misfolding and accumulation of proteins is the hallmark of polyQ-SCA types (see Table 1), however, also repeat-containing RNA may aggregate as for example is seen in SCA8, 31, and 36 [13-15]. These so-called RNA-foci accumulate in PCs and sequester RNA binding proteins that in the long run will affect RNA splicing, translational regulation, and other effects leading to neurotoxicity. Additionally, transcriptional dysregulation contributed to PC loss and cerebellar dysfunction due to loss of ataxin-1 function (SCA1) [16], and polyQ-expanded ataxin-3 (SCA3) [17]. The C-terminal part of the $Ca_v2.1$ subunit (α1ACT; SCA6) containing a normal poly-Q tract length is a transcription factor mediating transcription of several PC genes and rescued the pathology of SCA6 mouse [18]. Similarly to α1ACT, ataxin-7 (SCA7) as an integral subunit of the TATA-box binding protein (TBP)- free TBP associated factors (TAF) complex [19] and TBP (SCA17) also directly regulate transcription (reviewed in 20). Dysregulation of calcium signaling in PCs is one of the major disease mechanisms unerlying conventional SCA types caused by 1) mutations in voltage-gated calcium channels including *CACNA1A* (SCA6) and *CACNA1G* (SCA42) [21,22]) and voltage-gated potassium channels *KCNC3* (SCA13) and *KCND3* (SCA19/22) [5,6,23], 2) by mediating calcium release from intracellular stores as seen in SCA15/16/29 due to mutations in *ITPR1* encoding the InsP3 receptor type 1 or 3) regulation of mitochondrial calcium influx controlled by AFG3 Like Matrix AAA Peptidase Subunit 2 encoded by *AFG3L2* (SCA28) [24-27]. In the end, all these underlying mechanisms are suggested to evidently lead to early synaptic neurotransmission deficits and progressive

cerebellar dysfunction that are ultimately the causes of the pervasive loss of PCs resulting in SCA. Given that many reviews were published on these consensus disease mechanisms they will not be the focus of this work.

Some of the reported SCA genes do not fit into the consensus disease mechanisms listed above, demonstrating that other disease mechanisms may play a role in the SCA pathogenesis. To better understand how and why so many genetic insults can lead to pervasive PC degeneration and SCA, we need to understand what makes PCs so vulnerable for particular genetic insults compared to other neurons in the cerebellum such as granule cells, stellate and basket cells, or Bergman glia cells, and astrocytes.

Purkinje cells and SCA

PCs are large pear-shaped neuronal cells characterized by a large dendritic arbor decorated with thousands of little spines and a single axon originating from the other end. PC somas align in the cerebellar cortex to form the PC layer that lies in between the outer molecular layer, and inner granular cell layer. PCs integrate the large number of input signals from the parallel fibers (PF) of granule cells and climbing fibers (CF) coming out of the inferior olivary nucleus, and conveys the sole output signal from the cerebellar cortex to the deep cerebellar nuclei (DCN), which sends projections back to the brainstem and the cerebral cortex via the thalamus. This loop is called the cerebellar cortex–DCN–thalamus–cerebral cortex feedback loop (for recent reviews of cerebellar architecture and function see 28,29). The interaction of PC-CF and PC-PF inputs generates a unique form of heterosynaptic plasticity in PCs that has been shown to underlie motor learning (reviewed in 30). PCs provide the signals that are required for planning, performing and fine-tuning of movement and coordination, and consequently dysfunction and/or loss of PCs leads to cerebellar ataxia.

The question remains why PCs are vulnerable for the many genetic insults leading to SCA? The answer may lay in the unique structure of PCs with its large cell body and their

noticeable dendritic three with many branching extensions. Dendritic arborization is amongst others regulated by mitochondrial fission and mitochondrial transport [31], implying that proper regulation of energy supply is important for the developing dendritic tree of PCs. Vise versa, maintaining proper energy supply is important for PC survival as altered mitochondrial dynamics led to PC degeneration in SCA3 mouse [32] and alterations in the bioenergetic machinery was observed in SCA1 mouse cerebella [33]. Additionally, mutations in *AFG3L2* encoding AFG3-like AAA ATPase 2 cause SCA28 and loss of the m-AAA protease resulted in the accumulation of the mitochondrial Ca^{2+} uniporter MCU leading to mitochondrial calcium overload and subsequently neurodegeneration [27,34]. Another hallmark of PCs is their highly intrinsic activity and spontaneous action potential firing in the absence of synaptic input. Alterations in spontaneous PC firing has been seen in several SCA mouse models and other mouse models exhibiting ataxia due to mutations in genes important for PC and cerebellar functioning (reviewed in 35). Nevertheless, the exact molecular mechanisms underlying the pervasive PC vulnerability in SCA remains yet unknown.

Purkinje cell-enriched pathways

Comparative analysis can provide insights into cell-type specific and enriched transcripts for each cell population and at such can be used to identify intrinsic molecular components and corresponding pathways that could play a role in the specific neuronal degeneration. We hypothesized that by identifying PC specific genes we are able to highlight pathways that may give clues into the molecular mechanisms what makes PCs different from other neurons and glia in the cerebellum and why so many genetic insults can lead to PC degeneration in SCA. We made use of a publically available data set generated by Doyle et al [36]. In this study, transcription profiles of 24 CNS cell populations were generated using a Translating Ribosome Affinity Purification (TRAP) approach and were used in a complex comparative analysis to unravel the cellular and molecular complexity of the CNS. Not surprisingly, PCs

did not cluster strongly with other cell types. By a comparative analysis using data presented in Table S5 from Doyle *et al*., we identified 1029 PC-specific genes as they were not detected in cerebellar granule cells, cerebellar golgi cells, mature cerebellar oligodendrocytes (Cmtm5), a mixed mature and progenitor cerebellar oligodendrocyte population (Olig2), and cerebellar astrocytes (Figure 1 and Supplementary Tables 1). Using the DAVID gene accession conversion tool, we were able to convert these 1029 mouse transcripts to 491 human genes (Supplementary Table 2). This list of unique PC genes contained the known SCA genes *ITPR1*, *AFG3L2*, *TRPC3*, and *CACNA1G*, suggesting that these genes are functionally very important for PCs and further validates their role in the pathogenesis of SCA. Notably, all four genes are regulators of intracellular neuronal calcium homeostasis by either controlling mitochondrial calcium uptake (*AFG3L2*)[37,38], release of calcium from post-synaptic endoplasmatic reticulum stores (*ITPR1*) [39], regulating mGluR1-mediated calcium signaling (*TRPC3*) [40], and contribute to fast calcium signaling within PC dendritic spines (*CACNA1G*) [41]. Balanced calcium signaling is evidently crucial for neuronal functioning but also for neuronal survival as is shown by the increasing number of genetic mutations in calcium-mediating proteins causing neurodegenerative disorders including SCA and episodic ataxias (reviewed in 42). This observation further substantiates altered calcium homeostasis as an emerging shared pathway in the pathogenesis of SCA. Additionally, we performed a pathway analysis using the web-tool ConsensusPathDB [43] and this program predicted 4 pathways to be enriched in PCs using the unique PC transcripts as seeds (p-value < 0.0005)(Table 2) including 1) phosphatidylinosytol signaling system and inositol phosphate metabolism, 2) Huntington's disease, 3) (p38) MAPK signaling, and 4) nuclear receptor signaling. In the next section, we will discuss these biological pathways and their potential role in PC function and viability, and SCA pathogenesis.

Phosphatidylinosytol signaling system and inositol phosphate metabolism

PC activity is dependent of phosphatidylinositol signaling, as the inositol trisphosphate receptor type 1 (InsP3R1/*ITPR1*)(Table 2) is the key receptor in PCs that regulates the interaction between CF and PF inputs on PC dendrites and thus links the different levels of synaptic activity of long term potentiation to long term depression (LTD). In contrast to other neurons that use ryanodine receptors to release calcium from intracellular stores, PCs exhibit dense concentrations of InsP3R1 on their post-synaptic ER stores [39]. InsP3R1 mediates local calcium release via binding to the second messenger inositol 1,4,5-trisphosphate (IP3) that induces complex spatiotemporal patterns of calcium waves and oscillations required for the induction of LTD [44]. The crucial role of InsP3R1-mediated calcium signaling in PCs is underscored by the fact that deletions in *ITPR1* induce ataxia in mice and SCA15/SCA16 in humans [24]. The complexity of InsP3R1-mediated calcium signaling is further illustrated by the identification of recessive truncating mutations and/or de novo mutations in *ITPR1* underlying Gilespie syndrome characterized by congenital ataxia, intellectual disability and iris hypoplasia [45]. Recently, mutations were identified in *GRM1* encoding the metabotrophic glutamate receptor mGluR1 that triggers IP3 production upon PF stimulation to cause SCA44 [46]. Functional impairment of mGluR1 signaling was also observed in mouse SCA3 PCs [47], and mGluR1 mutant mice showed pronounced motor deficits, ataxic features and were deficient in cerebellar LTD affecting motor learning [48]. Mouse exhibiting mutant Inpp4a and Inpp5a (Table 2), encoding inositol 4/5-phosphatases catalyzing the removal of the 4/5-position phosphate from IP3 facilitating IP3 inactivity, exhibit severe ataxia, lethality (only the Inpp4a^{wbl} mice), and PC degeneration [49,50]. In addition, a mutation in ring finger protein 170 (*RNF170*) causes a dominant inherited sensory ataxia [51]. RNF170 was shown to mediate the ubiquitination of InsP3R1 and

cells expressing mutant RNF170 showed reduced Ca^{2+} mobilization that was not due to altered IP3 production or InsP3R1 ubiquitination [52]. How mutant RNF170 alters InsP3R1-mediated calcium signaling and if this is the cause of the PC degeneration seen in patient s remains to be investigated.

Despite its clearly crucial role in PCs, InsP3R1-mediated calcium signaling also has been reported to play a role in pathogenesis of the neurodegenerative disorders presenilin-linked familial Alzheimer's disease (AD), sporadic amyotrophic lateral sclerosis (ALS), and Huntington's disease (HD) [53-55]. This finding shows that InsP3R1-mediated calcium signaling is also important in regulating the survival of other neuronal cell types and therefore, cannot by itself explain why so many genetic insults lead to pervasive PC degeneration seen in SCA.

Huntington's disease

Huntington Disease (HD) is like SCA an autosomal dominant neurodegenerative disorder caused by a coding polyQ-repeat expansion in the Huntingtin (HTT) gene. The disease affects mainly neurons in the striatum, basal ganglia and the cortex. However, evidence is accumulating for a role of the cerebellum and PCs in early HD pathology. Cerebellar atrophy as well as PC loss was observed in HD postmortem tissue that did not correlate with the level of striatal atrophy [56], suggesting that the cerebellar atrophy is an independent event in HD pathogenesis. Marked PCs loss was detected in a juvenile HD mouse model (R6/2) at 12 weeks of age as well in a knock-in mouse model of HD (HdhQ200) that coincided with PC dysfunction [57]. In the end, the loss of PCs in the cerebellum might explain the ataxia, dysarthria, gait abnormalities and imbalance of the stature seen in many HD patients.

The HTT protein is involved in several important processes in neurons, amongst other in regulation of endocytosis, neuronal secretion and intracellular transport of Brain-derived Neuronal Factor (BDNF). BDNF knockout mouse display cerebellar pathology [58]

that very much resembled the pathology seen in *stargazer* (*stg*) mouse exhibiting a severe ataxia [59]. Remarkably, a selective defect in BDNF expression was observed in the cerebella of *stg* mouse and overexpression of BDNF was able to alleviate the ataxic symptoms and restored cerebellar architecture of *stg* mouse [60]. In SCA6 human cerebellum decreased levels of *BDNF* mRNA were observed that coincided with BDNF-immunoreactive granules in the dendrites of SCA6 PCs [61]. Mutant HTT was also reported to activate N-methyl-aspartate (NDMA) receptors via sensitizing InsP3R1 (Table 2) to IP3 via its interaction with the C-terminus of InsP3R1 [55,62]. Both mutant ataxin-2 and ataxin-3 proteins containing polyQ-repeat expansions were also found to bind to the C-terminus of InsP3R1 leading to its sensitization to activation by IP3 [63,64]. These findings highlight deranged InsP3R1-mediated Ca^{2+} signaling as an important pathway underlying the pervasive PC degeneration in SCA.

Additionally, many studies reported dysfunctional handling of Ca^{2+} load in mitochondria isolated from HD patients and from different HD mouse (reviewed in 65,66). Defects in the mitochondrial respiratory chain affecting the complexes II and IV of R6/2 mice *in vitro*, whereas defects in complex 1 have also been described in the muscles of HD patients [67,68]. Several of these complex I protein members including *NDUFA6*, *NDUFC1*, *NDUFA4*, *NDUFA2* showed relatively restricted expression to PCs (Table 2). Not surprisingly, it has become quite evident that mitochondrial dysfunction and bioenergetic perturbation leads to dysfunction of the spinocerebellar system and have been reported as a frequent cause underlying the pervasive PC degeneration in SCA. Mitochondrial dysfunction in relation to SCA will not be further discussed in this work.

Mutant HTT interacts and/or sequesters and thereby reduces the normal function of several transcription factors including TBP (SCA17) (Table 2) [69]. Moreover, HTT may act by itself as transcription factor by mimicking the action of glutamine-rich transcription factors

leading to transcriptional changes [70,71], and subsequently mutant HTT leads to transcriptional abnormalities. Interestingly, several Huntington-like cases indistinguishable from "real" HD but with cerebellar ataxia carried an expanded polyQ-repeat in the *TPB* gene [72]. Whether HD and SCA17 exhibit similar transcriptional changes need to be investigated but these studies may suggest an overlap in pathogenesis between HD and SCA.

(p38) MAPK signaling

Mitogen-activated protein kinases (MAPKs) signaling is a key process that regulates numerous cellular processes including proliferation, differentiation, apoptosis, and survival (reviewed in 73), and its activation is highly dependent on intracellular calcium levels. Many genes directly or indirectly involved in calcium signaling seem to have a restricted expression in PCs including *CACNB2*, *PRKCA*, *CACNG2*, *CACNA1G*, *MKNK1*, *MAPKAPK2*, *PTPRR* and others (Table 2). Several MAPK cascades have been identified of which extracellular signal-regulated kinseses-1 and -2 (ERK1 and ERK2) are the most studied but also include c-Jun N-terminal kinases (JNKs), and p38 MAPK. Interestingly, upstream regulators such as Ras, protein kinase C gamma (PKCγ), protein tyrosine phosphatases (PTPRR) and several downstream targets of ERKs are highly expressed in mature postmitotic neurons and/or in PCs. ERK activation is amongst other regulated by excitatory glutamatergic signaling [74,75], a pathway recognized to play a crucial role in the pathogenesis of SCA [11]. Recently, it was shown that MAPK/ERK regulates Group 1 metabotrophic glutamate receptors (mGluR1 and mGluR5) and modifies the cell surface expression of these receptors via site-specific phosphorylation [76]. This interaction between ERK and mGluR1 occurs at synaptic sites and apparently plays an essential role in synaptic plasticity by controlling LTP and spatial memory. The role of the MAPK signaling and synaptic plasticity is reviewed in [77].

Several components of the Ras–MAPK–MSK1 pathway including ERKs were reported to regulate ataxin-1 protein levels and thereby modulate neurotoxicity in SCA1 as

neurodegeneration was suppressed upon silencing of these components in both *Drosophila* and mice [78]. Additionally, aberrant MAPK signaling via reduced ERK phosphorylation and compromised nuclear translocation of ERK was shown to underlie SCA14 [79]. Given the essential role of PKC in cerebellar LTD [80,81], SCA14 PCs showed impaired pruning of CF synapses and failure of LTD expression affecting synaptic plasticity [82]. Increased phosphorylation levels of ERKs were detected brain tissue of mouse lacking all four PTPRR isoforms which are predominantly expressed in the PCs [83]. These *Ptprr* knockout mice developed problems with fine motor coordination, grip, and balance without obvious morphological changes in brain and PC morphology up to 20 months of age. Additionally, these mice exhibit impaired cerebellar LTD that was correlated to deficient a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) phosphorylation and internalization [84]. These datasets further underscore a role for MAPK signaling in regulating cerebellar motor function and suggest that MAPK/ERK signaling is required for PC function in cerebellar LTD and that abnormal MAPK/ERK signaling may lead to PC dysfunction rather than PC degeneration.

The p38 MAPK cascade might regulate a distinct form of synaptic plasticity contributing to LTD compared to MAPK/ERK signaling and involves the activation of NMDA-Rs and mGluRs [85,86]. p38 MAPK was shown to control associative learning, as a specific inhibitor of p38 infused in the cerebellar vermis prevented classical eye-blink conditioning [87]. Both paired and unpaired eye-blink conditioning affected PC morphology causing reduced dendritic tree length and size, and reduced number of spiny branch arbors [88]. Notably, defects in the acquisition of classical eye-blink conditioning were also reported in the severely ataxic *stg* mouse [89], linking the p38 MAPK cascade to cerebellar motor function and ataxia.

Nuclear receptor signaling

Nuclear receptors are ligand-activated transcription factors that play a key role in metabolic and developmental pathways regulate cellular processes including lipid and glucose homeostasis, detoxification, and differentiation [90]. Nuclear receptors also play key roles in the central nervous system since the brain has a very high lipid content and is metabolically very active (reviewed in 91). The most abundant nuclear receptors in the brain are peroxisome proliferation-activated receptors (PPARs) and liver X receptors (LXRs) that function as lipid and cholesterol sensors, respectively, and couple the size of the metabolic machinery to metabolic demand. However, other (inter-) nuclear receptors are also expressed in brain and PCs and include retinoid-related orphan receptor α (*RORA*), progesterone receptors (*PGR*) also called nuclear receptor subfamily 3 group C, member 3 (*NR3C3*), orphan nuclear receptor (*NR3B2/ESRRB*) and TR4 orphan receptor (*NR2C2*), nuclear receptor subfamily 2 group F, member 6 and 2 (*NR2F6* and *NR2F2*)(Table 2).

The importance of lipid homeostasis in PC functioning and survival is underscored by the fact that mutations in *ELOVL5*, and *ELOVL4* encoding elongases 4 and 5, involved in the synthesis of very-long-chain fatty acids with more than 16 carbons cause SCA34 and SCA38 [92,93]. Additionally, SCA genes *FAT1* and *FAT2* [94] were shown to promote omega-3 long-chain polyunsaturated fatty acids synthesis in transgenic fish expressing humanized *fat1* and *fat2* genes [95]. Furthermore, alkanine ceremidase 3 (Acer3) a precursor of the bioactive lipid sphingosine-1-phosphate (S1P) plays a crucial role in PC development as *Acer3* knockout mouse suffered from premature PC degeneration and cerebellar ataxia. Acer3 deficiency led to accumulation of total levels of ceremides and dyshomeostasis of their sphingolipid derivatives including S1P in the cerebellum [96]. Supporting evidence that proper control of ceremide biosynthesis is necessary to control PC viability is given by the fact that spontaneous mutations in *Lass1* encoding (dihydroc)ceramide synthase 1 caused PC degeneration due to abnormal dendritic development and subsequently ataxia [97].

Upon administration of a LXR receptor agonist, increased dendritic tree growth of PCs and migration of granule cell neurons was observed during cerebellum development [98]. In contrast, genetic ablation of LXRs caused deficits in motor coordination, spatial learning and myelination in the cerebellum that was not caused by large morphological structural changes or degeneration of cerebellum of LXRβ knockout mice but rather was due to loss of motor neurons in the spinal cord mimicking features seen in amyotrophic lateral sclerosis (ALS) [99,100].

Staggerer mice with severe ataxia and not well-developed PCs were shown to carry a spontaneous deletion in *Rora* encoding RORα (Table 2)[101]. Rorα deficient mice validated Rorα's role in the development of the cerebellum and PCs as these mice displayed motor deficits that were almost identical to *staggerer* mouse [102]. Anatomically both mice models revealed identical abnormalities that included a small cerebellum with a thin molecular layer and an almost absent granule cell layer. Furthermore, PCs were not aligned in a monolayer and exhibited small undifferentiated dendrites without small spine branches and were still innervated by multiple CFs [102,103]. Altered expression of Rorα target genes and reduced Rorα protein levels were observed in presymptomatic SCA1 mouse [104]. Additionally, partial loss of Rorα led to a more severe SCA1 disease phenotype and pathology. Reduced Rorα protein levels and reduced *Rora* mRNA levels were also seen in mouse SCA3 PCs and mouse ataxin2 knockout and ataxin2-CAG43 knockin cerebella, respectively [47,105]. Therefore, the abnormal phenotypes in the cerebella of the SCA2 and SCA3 mice may very likely be the result of aberrant Rorα-mediated transcription.

Interestingly, Rorα regulates the expression of numerous key genes in the developing cerebellum involved in calcium signaling including *Pcp4*, *Itpr1*, *Cals1*, and *Calb1* [106] and reduced levels of these targets were found before the onset of PC loss in *staggerer* mouse. This suggests that these gene expression changes are not a secondary effect of the pathogenesis [107].

This latter data implies that key events such as proper RORα expression during PC development plays a crucial role in the susceptibility of PCs and again highlights calcium-dependent pathways as proposed molecular mechanisms in SCA.

General conclusions and perspectives

Only two decades after the discovery of the first genetic cause of SCA, technological advances in genetics has led to the rapid identification of over 35 functionally diverse SCA genes. The question why do so many genetic insults lead to pervasive PC degeneration and SCA remains yet partly unanswered. However, others and we suggest that the answer to this question lies within the unique characteristics of PCs compared to other neurons in the cerebellum. Therefore, it is crucial to increase our understanding of these underlying molecular mechanisms and corresponding pathways that are fundamental for dysfunction and degeneration of PCs in SCA.

In this review, we discussed the current knowledge on the consensus mechanisms underlying SCA and highlighted specific pathways that are very likely crucial for PC function using publically available cell type specific expression data. The pathways that were identified during our analysis included phosphatidylinositol signaling system and inositol phosphate metabolism, Huntington's disease, (p38) MAPK signaling, and nuclear receptor signaling and seemingly all converge onto intracellular calcium homeostasis. Another study identified 2 SCA transcript-enriched modules in control (non-SCA) postmortem cerebellar tissue by investigating regional differences in gene expression [108]. One of these modules contained several transcripts involved in calcium signaling also pointing towards an important role of calcium-mediated signaling in the pathogenesis of SCA. Generally, we hypothesize that any genetic insult that may alter directly or indirectly intracellular calcium levels of PCs is likely to cause PC dysfunction followed by degeneration and SCA.

The list of unique PC genes may very likely contain candidate disease genes for genetically undiagnosed SCA cases or may contain disease modifiers. This is nicely illustrated by the observation that elevated levels of PC-specific gene Cck Supplementary Table 2) encoding cholecystokinin was shown to activate a neuroprotective pathway via binding to Cck1R in the cerebella of Atxn1-[30Q]-D776 transgenic mice preventing progressive PC degeneration [109]. The identification of key pathways specific for PC function and survival using unbiased approaches will help to direct future studies on interfering with the molecular mechanisms of neurotoxicity in different stages of the disease.

Conflict of interest

None reported

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URLs

Venn Diagram analysis was provided by the Bioinformatics and Systems Biology of Gent, http://bioinformatics.psb.ugent.be/webtools/Venn;

ConsensusPathDB, http://consensuspathdb.org

DAVID gene accession conversion tool, https://david.ncifcrf.gov/conversion.jsp

References

[1] A. Durr, Autosomal dominant cerebellar ataxias: polyglutamine expansions and beyond, Lancet Neurol. 9 (2010) 885–894. doi:10.1016/S1474-4422(10)70183-6.

[2] T. Klockgether, Update on degenerative ataxias, Curr. Opin. Neurol. 24 (2011) 339–345. doi:10.1097/WCO.0b013e32834875ba.

[3] H. Kobayashi, K. Abe, T. Matsuura, Y. Ikeda, T. Hitomi, Y. Akechi, et al., Expansion of intronic GGCCTG hexanucleotide repeat in NOP56 causes SCA36, a type of spinocerebellar ataxia accompanied by motor neuron involvement, Am. J. Hum.

Genet. 89 (2011) 121–130. doi:10.1016/j.ajhg.2011.05.015.

[4] A.I. Seixas, J.R. Loureiro, C. Costa, A. Ordóñez-Ugalde, H. Marcelino, C.L. Oliveira, et al., A Pentanucleotide ATTTC Repeat Insertion in the Non-coding Region of DAB1, Mapping to SCA37, Causes Spinocerebellar Ataxia, Am. J. Hum. Genet. 101 (2017) 87–103. doi:10.1016/j.ajhg.2017.06.007.

[5] A. Duarri, J. Jezierska, M. Fokkens, M. Meijer, H.J. Schelhaas, W.F.A. den Dunnen, et al., Mutations in potassium channel kcnd3 cause spinocerebellar ataxia type 19, Ann. Neurol. 72 (2012) 870–880. doi:10.1002/ana.23700.

[6] Y.-C. Lee, A. Durr, K. Majczenko, Y.-H. Huang, Y.-C. Liu, C.-C. Lien, et al., Mutations in KCND3 cause spinocerebellar ataxia type 22, Ann. Neurol. 72 (2012) 859–869. doi:10.1002/ana.23701.

[7] B.L. Fogel, S.M. Hanson, E.B.E. Becker, Do mutations in the murine ataxia gene TRPC3 cause cerebellar ataxia in humans? Mov. Disord. 30 (2015) 284–286. doi:10.1002/mds.26096.

[8] G. Bakalkin, H. Watanabe, J. Jezierska, C. Depoorter, C. Verschuuren-Bemelmans, I. Bazov, et al., Prodynorphin mutations cause the neurodegenerative disorder spinocerebellar ataxia type 23, Am. J. Hum. Genet. 87 (2010) 593–603. doi:10.1016/j.ajhg.2010.10.001.

[9] S. Schorge, J. van de Leemput, A. Singleton, H. Houlden, J. Hardy, Human ataxias: a genetic dissection of inositol triphosphate receptor (ITPR1)-dependent signaling, Trends in Neurosciences. 33 (2010) 211–219. doi:10.1016/j.tins.2010.02.005.

[10] D.S. Verbeek, B.P.C. van de Warrenburg, Genetics of the dominant ataxias, Semin Neurol. 31 (2011) 461–469. doi:10.1055/s-0031-1299785.

[11] A. Matilla-Dueñas, T. Ashizawa, A. Brice, S. Magri, K.N. McFarland, M. Pandolfo, et al., Consensus paper: pathological mechanisms underlying neurodegeneration in spinocerebellar ataxias, in: Cerebellum, 2014: pp. 269–302. doi:10.1007/s12311-013-0539-y.

[12] K.E. Hekman, C.M. Gomez, The autosomal dominant spinocerebellar ataxias: emerging mechanistic themes suggest pervasive Purkinje cell vulnerability, J Neurol Neurosurg Psychiatry. 86 (2015) 554–561. doi:10.1136/jnnp-2014-308421.

[13] I.-C. Chen, H.-Y. Lin, G.-C. Lee, S.-H. Kao, C.-M. Chen, Y.-R. Wu, et al., Spinocerebellar ataxia type 8 larger triplet expansion alters histone modification and induces RNA foci, BMC Mol. Biol. 10 (2009) 9. doi:10.1186/1471-2199-10-9.

[14] Y. Niimi, M. Takahashi, E. Sugawara, S. Umeda, M. Obayashi, N. Sato, et al., Abnormal RNA structures (RNA foci) containing a penta-nucleotide repeat (UGGAA)n in the Purkinje cell nucleus is associated with spinocerebellar ataxia type 31 pathogenesis, Neuropathology. 33 (2013) 600–611. doi:10.1111/neup.12032.

[15] W. Liu, Y. Ikeda, N. Hishikawa, T. Yamashita, K. Deguchi, K. Abe, Characteristic RNA foci of the abnormal hexanucleotide GGCCUG repeat expansion in spinocerebellar ataxia type 36 (Asidan), Eur. J. Neurol. 21 (2014) 1377–1386.

doi:10.1111/ene.12491.

[16] J. Crespo-Barreto, J.D. Fryer, C.A. Shaw, H.T. Orr, H.Y. Zoghbi, Partial loss of ataxin-1 function contributes to transcriptional dysregulation in spinocerebellar ataxia type 1 pathogenesis, PLoS Genet. 6 (2010) e1001021. doi:10.1371/journal.pgen.1001021.

[17] A.-H. Chou, T.-H. Yeh, P. Ouyang, Y.-L. Chen, S.-Y. Chen, H.-L. Wang, Polyglutamine-expanded ataxin-3 causes cerebellar dysfunction of SCA3 transgenic mice by inducing transcriptional dysregulation, Neurobiol. Dis. 31 (2008) 89–101. doi:10.1016/j.nbd.2008.03.011.

[18] X. Du, J. Wang, H. Zhu, L. Rinaldo, K.-M. Lamar, A.C. Palmenberg, et al., Second cistron in CACNA1A gene encodes a transcription factor mediating cerebellar development and SCA6, Cell. 154 (2013) 118–133. doi:10.1016/j.cell.2013.05.059.

[19] D. Helmlinger, S. Hardy, S. Sasorith, F. Klein, F. Robert, C. Weber, et al., Ataxin-7 is a subunit of GCN5 histone acetyltransferase-containing complexes, Hum. Mol. Genet. 13 (2004) 1257–1265. doi:10.1093/hmg/ddh139.

[20] S. Yang, X.-J. Li, S. Li, Molecular mechanisms underlying Spinocerebellar Ataxia 17 (SCA17) pathogenesis, Rare Dis. 4 (2016) e1223580. doi:10.1080/21675511.2016.1223580.

[21] O. Zhuchenko, J. Bailey, P. Bonnen, T. Ashizawa, D.W. Stockton, C. Amos, et al., Autosomal dominant cerebellar ataxia (SCA6) associated with small polyglutamine expansions in the alpha 1A-voltage-dependent calcium channel, Nat. Genet. 15 (1997) 62–69. doi:10.1038/ng0197-62.

[22] M. Coutelier, I. Blesneac, A. Monteil, M.-L. Monin, K. Ando, E. Mundwiller, et al., A Recurrent Mutation in CACNA1G Alters Cav3.1 T-Type Calcium-Channel Conduction and Causes Autosomal-Dominant Cerebellar Ataxia, Am. J. Hum. Genet. 97 (2015) 726–737. doi:10.1016/j.ajhg.2015.09.007.

[23] M.F. Waters, N.A. Minassian, G. Stevanin, K.P. Figueroa, J.P.A. Bannister, D. Nolte, et al., Mutations in voltage-gated potassium channel KCNC3 cause degenerative and developmental central nervous system phenotypes, Nat. Genet. 38 (2006) 447–451. doi:10.1038/ng1758.

[24] J. van de Leemput, J. Chandran, M.A. Knight, L.A. Holtzclaw, S. Scholz, M.R. Cookson, et al., Deletion at ITPR1 underlies ataxia in mice and spinocerebellar ataxia 15 in humans, PLoS Genet. 3 (2007) e108. doi:10.1371/journal.pgen.0030108.

[25] A. Iwaki, Y. Kawano, S. Miura, H. Shibata, D. Matsuse, W. Li, et al., Heterozygous deletion of ITPR1, but not SUMF1, in spinocerebellar ataxia type 16, J. Med. Genet. 45 (2008) 32–35. doi:10.1136/jmg.2007.053942.

[26] L. Huang, J.W. Chardon, M.T. Carter, K.L. Friend, T.E. Dudding, J. Schwartzentruber, et al., Missense mutations in ITPR1 cause autosomal dominant congenital nonprogressive spinocerebellar ataxia, Orphanet J Rare Dis. 7 (2012) 67. doi:10.1186/1750-1172-7-67.

[27] D. Di Bella, F. Lazzaro, A. Brusco, M. Plumari, G. Battaglia, A. Pastore, et al., Mutations in the mitochondrial protease gene AFG3L2 cause dominant hereditary ataxia SCA28, Nat. Genet. 42 (2010) 313–321. doi:10.1038/ng.544.

[28] N.L. Cerminara, E.J. Lang, R.V. Sillitoe, R. Apps, Redefining the cerebellar cortex as an assembly of non-uniform Purkinje cell microcircuits, Nat Rev Neurosci. 16 (2015) 79–93. doi:10.1038/nrn3886.

[29] E. Galliano, C.I. De Zeeuw, Questioning the Cerebellar Doctrine, in: Cerebellar Learning, Elsevier, 2014: pp. 59–77. doi:10.1016/B978-0-444-63356-9.00003-0.

[30] E. D'Angelo, L. Mapelli, C. Casellato, J.A. Garrido, N. Luque, J. Monaco, et al., Distributed Circuit Plasticity: New Clues for the Cerebellar Mechanisms of Learning, Cerebellum. 15 (2016) 139–151. doi:10.1007/s12311-015-0711-7.

[31] K. Fukumitsu, T. Hatsukano, A. Yoshimura, J. Heuser, K. Fujishima, M. Kengaku, Mitochondrial fission protein Drp1 regulates mitochondrial transport and dendritic arborization in cerebellar Purkinje cells, Mol. Cell. Neurosci. 71 (2016) 56–65. doi:10.1016/j.mcn.2015.12.006.

[32] J.-Y. Hsu, Y.-L. Jhang, P.-H. Cheng, Y.-F. Chang, S.-H. Mao, H.-I. Yang, et al., The Truncated C-terminal Fragment of Mutant ATXN3 Disrupts Mitochondria Dynamics in Spinocerebellar Ataxia Type 3 Models, Front Mol Neurosci. 10 (2017) 196. doi:10.3389/fnmol.2017.00196.

[33] I. Sánchez, E. Balagué, A. Matilla-Dueñas, Ataxin-1 regulates the cerebellar bioenergetics proteome through the GSK3β-mTOR pathway which is altered in Spinocerebellar ataxia type 1 (SCA1), Hum. Mol. Genet. 25 (2016) 4021–4040. doi:10.1093/hmg/ddw242.

[34] T. König, S.E. Tröder, K. Bakka, A. Korwitz, R. Richter-Dennerlein, P.A. Lampe, et al., The m-AAA Protease Associated with Neurodegeneration Limits MCU Activity in Mitochondria, Mol. Cell. 64 (2016) 148–162. doi:10.1016/j.molcel.2016.08.020.

[35] P. Meera, S.M. Pulst, T.S. Otis, Cellular and circuit mechanisms underlying spinocerebellar ataxias, The Journal of Physiology. 594 (2016) 4653–4660. doi:10.1113/JP271897.

[36] J.P. Doyle, J.D. Dougherty, M. Heiman, E.F. Schmidt, T.R. Stevens, G. Ma, et al., Application of a translational profiling approach for the comparative analysis of CNS cell types, Cell. 135 (2008) 749–762. doi:10.1016/j.cell.2008.10.029.

[37] F. Maltecca, E. Baseggio, F. Consolato, D. Mazza, P. Podini, S.M. Young, et al., Purkinje neuron Ca2+ influx reduction rescues ataxia in SCA28 model, J. Clin. Invest. 125 (2015) 263–274. doi:10.1172/JCI74770.

[38] F. Maltecca, D. De Stefani, L. Cassina, F. Consolato, M. Wasilewski, L. Scorrano, et al., Respiratory dysfunction by AFG3L2 deficiency causes decreased mitochondrial calcium uptake via organellar network fragmentation, Hum. Mol. Genet. 21 (2012) 3858–3870. doi:10.1093/hmg/dds214.

[39] S. Bardo, M.G. Cavazzini, N. Emptage, The role of the endoplasmic reticulum Ca2+ store in the plasticity of central neurons, Trends in Pharmacological Sciences. 27

(2006) 78–84. doi:10.1016/j.tips.2005.12.008.

[40] J. Hartmann, H.A. Henning, A. Konnerth, mGluR1/TRPC3-mediated Synaptic Transmission and Calcium Signaling in Mammalian Central Neurons, Cold Spring Harb Perspect Biol. 3 (2011) a006726–a006726. doi:10.1101/cshperspect.a006726.

[41] M.E. Hildebrand, P. Isope, T. Miyazaki, T. Nakaya, E. Garcia, A. Feltz, et al., Functional coupling between mGluR1 and Cav3.1 T-type calcium channels contributes to parallel fiber-induced fast calcium signaling within Purkinje cell dendritic spines, J. Neurosci. 29 (2009) 9668–9682. doi:10.1523/JNEUROSCI.0362-09.2009.

[42] M.D. Mark, J.C. Schwitalla, M. Groemmke, S. Herlitze, Keeping Our Calcium in Balance to Maintain Our Balance, Biochem. Biophys. Res. Commun. 483 (2017) 1040–1050. doi:10.1016/j.bbrc.2016.07.020.

[43] A. Kamburov, C. Wierling, H. Lehrach, R. Herwig, ConsensusPathDB--a database for integrating human functional interaction networks, Nucleic Acids Research. 37 (2009) D623–8. doi:10.1093/nar/gkn698.

[44] T. Inoue, K. Kato, K. Kohda, K. Mikoshiba, Type 1 inositol 1,4,5-trisphosphate receptor is required for induction of long-term depression in cerebellar Purkinje neurons, J. Neurosci. 18 (1998) 5366–5373.

[45] M. McEntagart, K.A. Williamson, J.K. Rainger, A. Wheeler, A. Seawright, E. De Baere, et al., A Restricted Repertoire of De Novo Mutations in ITPR1 Cause Gillespie Syndrome with Evidence for Dominant-Negative Effect, Am. J. Hum. Genet. 98 (2016) 981–992. doi:10.1016/j.ajhg.2016.03.018.

[46] L.M. Watson, E. Bamber, R.P. Schnekenberg, J. Williams, C. Bettencourt, J. Lickiss, et al., Dominant Mutations in GRM1 Cause Spinocerebellar Ataxia Type 44, Am. J. Hum. Genet. 101 (2017) 451–458. doi:10.1016/j.ajhg.2017.08.005.

[47] A. Konno, A.N. Shuvaev, N. Miyake, K. Miyake, A. Iizuka, S. Matsuura, et al., Mutant ataxin-3 with an abnormally expanded polyglutamine chain disrupts dendritic development and metabotropic glutamate receptor signaling in mouse cerebellar Purkinje cells, Cerebellum. 13 (2014) 29–41. doi:10.1007/s12311-013-0516-5.

[48] A. Aiba, M. Kano, C. Chen, M.E. Stanton, G.D. Fox, K. Herrup, et al., Deficient cerebellar long-term depression and impaired motor learning in mGluR1 mutant mice, Cell. 79 (1994) 377–388.

[49] A. Nystuen, M.E. Legare, L.D. Shultz, W.N. Frankel, A null mutation in inositol polyphosphate 4-phosphatase type I causes selective neuronal loss in weeble mutant mice, Neuron. 32 (2001) 203–212.

[50] A.W. Yang, A.J. Sachs, A.M. Nystuen, Deletion of Inpp5a causes ataxia and cerebellar degeneration in mice, Neurogenetics. 16 (2015) 277–285. doi:10.1007/s10048-015-0450-4.

[51] P.N. Valdmanis, N. Dupré, M. Lachance, S.J. Stochmanski, V.V. Belzil, P.A. Dion, et

al., A mutation in the RNF170 gene causes autosomal dominant sensory ataxia, Brain. 134 (2011) 602–607. doi:10.1093/brain/awq329.

[52] F.A. Wright, J.P. Lu, D.A. Sliter, N. Dupré, G.A. Rouleau, R.J.H. Wojcikiewicz, A Point Mutation in the Ubiquitin Ligase RNF170 That Causes Autosomal Dominant Sensory Ataxia Destabilizes the Protein and Impairs Inositol 1,4,5-Trisphosphate Receptor-mediated Ca2+ Signaling, J. Biol. Chem. 290 (2015) 13948–13957. doi:10.1074/jbc.M115.655043.

[53] D. Shilling, M. Müller, H. Takano, D.-O.D. Mak, T. Abel, D.A. Coulter, et al., Suppression of InsP3 receptor-mediated Ca2+ signaling alleviates mutant presenilin-linked familial Alzheimer's disease pathogenesis, J. Neurosci. 34 (2014) 6910–6923. doi:10.1523/JNEUROSCI.5441-13.2014.

[54] M.R. Pagani, R.C. Reisin, O.D. Uchitel, Calcium signaling pathways mediating synaptic potentiation triggered by amyotrophic lateral sclerosis IgG in motor nerve terminals, J. Neurosci. 26 (2006) 2661–2672. doi:10.1523/JNEUROSCI.4394-05.2006.

[55] T.-S. Tang, H. Tu, E.Y.W. Chan, A. Maximov, Z. Wang, C.L. Wellington, et al., Huntingtin and huntingtin-associated protein 1 influence neuronal calcium signaling mediated by inositol-(1,4,5) triphosphate receptor type 1, Neuron. 39 (2003) 227–239.

[56] U. Rüb, F. Hoche, E.R. Brunt, H. Heinsen, K. Seidel, D. Del Turco, et al., Degeneration of the cerebellum in Huntington's disease (HD): possible relevance for the clinical picture and potential gateway to pathological mechanisms of the disease process, Brain Pathol. 23 (2013) 165–177. doi:10.1111/j.1750-3639.2012.00629.x.

[57] S.E. Dougherty, J.L. Reeves, M. Lesort, P.J. Detloff, R.M. Cowell, Purkinje cell dysfunction and loss in a knock-in mouse model of Huntington disease, Exp. Neurol. 240 (2013) 96–102. doi:10.1016/j.expneurol.2012.11.015.

[58] P.M. Schwartz, R.L. Levy, P.R. Borghesani, R.A. Segal, Cerebellar pathology in BDNF -/- mice: the classic view of neurotrophins is changing, Mol. Psychiatry. 3 (1998) 116–120.

[59] X. Qiao, F. Hefti, B. Knusel, J.L. Noebels, Selective failure of brain-derived neurotrophic factor mRNA expression in the cerebellum of stargazer, a mutant mouse with ataxia, J. Neurosci. 16 (1996) 640–648.

[60] H. Meng, S.K. Larson, R. Gao, X. Qiao, BDNF transgene improves ataxic and motor behaviors in stargazer mice, Brain Res. 1160 (2007) 47–57. doi:10.1016/j.brainres.2007.05.048.

[61] M. Takahashi, K. Ishikawa, N. Sato, M. Obayashi, Y. Niimi, T. Ishiguro, et al., Reduced brain-derived neurotrophic factor (BDNF) mRNA expression and presence of BDNF-immunoreactive granules in the spinocerebellar ataxia type 6 (SCA6) cerebellum, Neuropathology. 32 (2012) 595–603. doi:10.1111/j.1440-1789.2012.01302.x.

[62] N. Chen, T. Luo, C. Wellington, M. Metzler, K. McCutcheon, M.R. Hayden, et al.,

Subtype-specific enhancement of NMDA receptor currents by mutant huntingtin, J. Neurochem. 72 (1999) 1890–1898.

[63] J. Liu, T.-S. Tang, H. Tu, O. Nelson, E. Herndon, D.P. Huynh, et al., Deranged calcium signaling and neurodegeneration in spinocerebellar ataxia type 2, J. Neurosci. 29 (2009) 9148–9162. doi:10.1523/JNEUROSCI.0660-09.2009.

[64] X. Chen, T.-S. Tang, H. Tu, O. Nelson, M. Pook, R. Hammer, et al., Deranged calcium signaling and neurodegeneration in spinocerebellar ataxia type 3, J. Neurosci. 28 (2008) 12713–12724. doi:10.1523/JNEUROSCI.3909-08.2008.

[65] M. Giacomello, R. Hudec, R. Lopreiato, Huntington's disease, calcium, and mitochondria, Biofactors. 37 (2011) 206–218. doi:10.1002/biof.162.

[66] G. Liot, J. Valette, J. Pépin, J. Flament, E. Brouillet, Energy defects in Huntington's disease: Why 'in vivo' evidence matters, Biochem. Biophys. Res. Commun. 483 (2017) 1084–1095. doi:10.1016/j.bbrc.2016.09.065.

[67] S.J. Tabrizi, J. Workman, P.E. Hart, L. Mangiarini, A. Mahal, G. Bates, et al., Mitochondrial dysfunction and free radical damage in the Huntington R6/2 transgenic mouse, Ann. Neurol. 47 (2000) 80–86.

[68] J. Arenas, Y. Campos, R. Ribacoba, M.A. Martín, J.C. Rubio, P. Ablanedo, et al., Complex I defect in muscle from patients with Huntington's disease, Ann. Neurol. 43 (1998) 397–400. doi:10.1002/ana.410430321.

[69] W.M.C. van Roon-Mom, S.J. Reid, A.L. Jones, M.E. MacDonald, R.L.M. Faull, R.G. Snell, Insoluble TATA-binding protein accumulation in Huntington's disease cortex, Brain Res. Mol. Brain Res. 109 (2002) 1–10.

[70] K.L. Sugars, D.C. Rubinsztein, Transcriptional abnormalities in Huntington disease, Trends Genet. 19 (2003) 233–238. doi:10.1016/S0168-9525(03)00074-X.

[71] C.L. Benn, T. Sun, G. Sadri-Vakili, K.N. McFarland, D.P. DiRocco, G.J. Yohrling, et al., Huntingtin modulates transcription, occupies gene promoters in vivo, and binds directly to DNA in a polyglutamine-dependent manner, J. Neurosci. 28 (2008) 10720–10733. doi:10.1523/JNEUROSCI.2126-08.2008.

[72] P. Bauer, F. Laccone, A. Rolfs, U. Wüllner, S. Bösch, H. Peters, et al., Trinucleotide repeat expansion in SCA17/TBP in white patients with Huntington's disease-like phenotype, J. Med. Genet. 41 (2004) 230–232. doi:10.1136/jmg.2003.015602.

[73] G. Pearson, F. Robinson, T. Beers Gibson, B.E. Xu, M. Karandikar, K. Berman, et al., Mitogen-activated protein (MAP) kinase pathways: regulation and physiological functions, Endocr. Rev. 22 (2001) 153–183. doi:10.1210/edrv.22.2.0428.

[74] R.S. Fiore, T.H. Murphy, J.S. Sanghera, S.L. Pelech, J.M. Baraban, Activation of p42 mitogen-activated protein kinase by glutamate receptor stimulation in rat primary cortical cultures, J. Neurochem. 61 (1993) 1626–1633.

[75] Z. Xia, H. Dudek, C.K. Miranti, M.E. Greenberg, Calcium influx via the NMDA receptor induces immediate early gene transcription by a MAP kinase/ERK-dependent mechanism, J. Neurosci. 16 (1996) 5425–5436.

[76] L.-M. Mao, J.Q. Wang, Regulation of Group I Metabotropic Glutamate Receptors by MAPK/ERK in Neurons, J Nat Sci. 2 (2016).

[77] G.M. Thomas, R.L. Huganir, MAPK cascade signalling and synaptic plasticity, Nat Rev Neurosci. 5 (2004) 173–183. doi:10.1038/nrn1346.

[78] J. Park, I. Al-Ramahi, Q. Tan, N. Mollema, J.R. Diaz-Garcia, T. Gallego-Flores, et al., RAS–MAPK–MSK1 pathway modulates ataxin 1 protein levels and toxicity in SCA1, Nature. 498 (2013) 325–331. doi:10.1038/nature12204.

[79] D.S. Verbeek, J. Goedhart, L. Bruinsma, R.J. Sinke, E.A. Reits, PKC gamma mutations in spinocerebellar ataxia type 14 affect C1 domain accessibility and kinase activity leading to aberrant MAPK signaling, J. Cell. Sci. 121 (2008) 2339–2349. doi:10.1242/jcs.027698.

[80] C.I. De Zeeuw, C. Hansel, F. Bian, S.K. Koekkoek, A.M. van Alphen, D.J. Linden, et al., Expression of a protein kinase C inhibitor in Purkinje cells blocks cerebellar LTD and adaptation of the vestibulo-ocular reflex, Neuron. 20 (1998) 495–508.

[81] J. Goossens, H. Daniel, A. Rancillac, J. van der Steen, J. Oberdick, F. Crépel, et al., Expression of protein kinase C inhibitor blocks cerebellar long-term depression without affecting Purkinje cell excitability in alert mice, J. Neurosci. 21 (2001) 5813–5823.

[82] A.N. Shuvaev, H. Horiuchi, T. Seki, H. Goenawan, T. Irie, A. Iizuka, et al., Mutant PKCγ in spinocerebellar ataxia type 14 disrupts synapse elimination and long-term depression in Purkinje cells in vivo, J. Neurosci. 31 (2011) 14324–14334. doi:10.1523/JNEUROSCI.5530-10.2011.

[83] R.G.S. Chirivi, Y.E. Noordman, C.E.E.M. Van der Zee, W.J.A.J. Hendriks, Altered MAP kinase phosphorylation and impaired motor coordination in PTPRR deficient mice, J. Neurochem. 101 (2007) 829–840. doi:10.1111/j.1471-4159.2006.04398.x.

[84] M. Erkens, K. Tanaka-Yamamoto, G. Cheron, J. Márquez-Ruiz, C. Prigogine, J.T. Schepens, et al., Protein tyrosine phosphatase receptor type R is required for Purkinje cell responsiveness in cerebellar long-term depression, Mol Brain. 8 (2015) 1. doi:10.1186/s13041-014-0092-8.

[85] J.J. Zhu, Y. Qin, M. Zhao, L. Van Aelst, R. Malinow, Ras and Rap control AMPA receptor trafficking during synaptic plasticity, Cell. 110 (2002) 443–455.

[86] V.Y. Bolshakov, L. Carboni, M.H. Cobb, S.A. Siegelbaum, F. Belardetti, Dual MAP kinase pathways mediate opposing forms of long-term plasticity at CA3-CA1 synapses, Nat. Neurosci. 3 (2000) 1107–1112. doi:10.1038/80624.

[87] X. Zhen, W. Du, A.G. Romano, E. Friedman, J.A. Harvey, The p38 mitogen-activated protein kinase is involved in associative learning in rabbits, J. Neurosci. 21 (2001) 5513–5519.

[88] B.J. Anderson, K. Relucio, K. Haglund, C. Logan, B. Knowlton, J. Thompson, et al., Effects of paired and unpaired eye-blink conditioning on Purkinje cell morphology, Learn. Mem. 6 (1999) 128–137.

[89] C.A. Richardson, B. Leitch, Cerebellar Golgi, Purkinje, and basket cells have

reduced gamma-aminobutyric acid immunoreactivity in stargazer mutant mice, J. Comp. Neurol. 453 (2002) 85–99. doi:10.1002/cne.10406.

[90] K. King-Jones, C.S. Thummel, Nuclear receptors--a perspective from Drosophila, Nat. Rev. Genet. 6 (2005) 311–323. doi:10.1038/nrg1581.

[91] R. Skerrett, T. Malm, G. Landreth, Nuclear receptors in neurodegenerative diseases, Neurobiol. Dis. 72 Pt A (2014) 104–116. doi:10.1016/j.nbd.2014.05.019.

[92] K. Ozaki, H. Doi, J. Mitsui, N. Sato, Y. Iikuni, T. Majima, et al., A Novel Mutation in ELOVL4 Leading to Spinocerebellar Ataxia (SCA) With the Hot Cross Bun Sign but Lacking Erythrokeratodermia: A Broadened Spectrum of SCA34, JAMA Neurol. 72 (2015) 797–805. doi:10.1001/jamaneurol.2015.0610.

[93] E. Di Gregorio, B. Borroni, E. Giorgio, D. Lacerenza, M. Ferrero, N. Lo Buono, et al., ELOVL5 mutations cause spinocerebellar ataxia 38, Am. J. Hum. Genet. 95 (2014) 209–217. doi:10.1016/j.ajhg.2014.07.001.

[94] E.A.R. Nibbeling, A. Duarri, C.C. Verschuuren-Bemelmans, M.R. Fokkens, J.M. Karjalainen, C.J.L.M. Smeets, et al., Exome sequencing and network analysis identifies shared mechanisms underlying spinocerebellar ataxia, Brain. (2017). doi:10.1093/brain/awx251.

[95] S.-C. Pang, H.-P. Wang, K.-Y. Li, Z.-Y. Zhu, J.X. Kang, Y.-H. Sun, Double transgenesis of humanized fat1 and fat2 genes promotes omega-3 polyunsaturated fatty acids synthesis in a zebrafish model, Mar. Biotechnol. 16 (2014) 580–593. doi:10.1007/s10126-014-9577-9.

[96] K. Wang, R. Xu, J. Schrandt, P. Shah, Y.Z. Gong, C. Preston, et al., Alkaline Ceramidase 3 Deficiency Results in Purkinje Cell Degeneration and Cerebellar Ataxia Due to Dyshomeostasis of Sphingolipids in the Brain, PLoS Genet. 11 (2015) e1005591. doi:10.1371/journal.pgen.1005591.

[97] L. Zhao, S.D. Spassieva, T.J. Jucius, L.D. Shultz, H.E. Shick, W.B. Macklin, et al., A deficiency of ceramide biosynthesis causes cerebellar purkinje cell neurodegeneration and lipofuscin accumulation, PLoS Genet. 7 (2011) e1002063. doi:10.1371/journal.pgen.1002063.

[98] Y. Xing, X. Fan, D. Ying, Liver X receptor agonist treatment promotes the migration of granule neurons during cerebellar development, J. Neurochem. 115 (2010) 1486–1494. doi:10.1111/j.1471-4159.2010.07053.x.

[99] D. Meffre, G. Shackleford, M. Hichor, V. Gorgievski, E.T. Tzavara, A. Trousson, et al., Liver X receptors alpha and beta promote myelination and remyelination in the cerebellum, Proc. Natl. Acad. Sci. U.S.a. 112 (2015) 7587–7592. doi:10.1073/pnas.1424951112.

[100] S. Andersson, N. Gustafsson, M. Warner, J.-A. Gustafsson, Inactivation of liver X receptor beta leads to adult-onset motor neuron degeneration in male mice, Proc. Natl. Acad. Sci. U.S.a. 102 (2005) 3857–3862. doi:10.1073/pnas.0500634102.

[101] B.A. Hamilton, W.N. Frankel, A.W. Kerrebrock, T.L. Hawkins, W. FitzHugh, K.

Kusumi, et al., Disruption of the nuclear hormone receptor RORalpha in staggerer mice, Nature. 379 (1996) 736–739. doi:10.1038/379736a0.

[102] M. Steinmayr, E. André, F. Conquet, L. Rondi-Reig, N. Delhaye-Bouchaud, N. Auclair, et al., staggerer phenotype in retinoid-related orphan receptor alpha-deficient mice, Proc. Natl. Acad. Sci. U.S.a. 95 (1998) 3960–3965.

[103] F. Boukhtouche, S. Janmaat, G. Vodjdani, V. Gautheron, J. Mallet, I. Dusart, et al., Retinoid-related orphan receptor alpha controls the early steps of Purkinje cell dendritic differentiation, J. Neurosci. 26 (2006) 1531–1538. doi:10.1523/JNEUROSCI.4636-05.2006.

[104] H.G. Serra, L. Duvick, T. Zu, K. Carlson, S. Stevens, N. Jorgensen, et al., RORalpha-mediated Purkinje cell development determines disease severity in adult SCA1 mice, Cell. 127 (2006) 697–708. doi:10.1016/j.cell.2006.09.036.

[105] M.V. Halbach, S. Gispert, T. Stehning, E. Damrath, M. Walter, G. Auburger, Atxn2 Knockout and CAG42-Knock-in Cerebellum Shows Similarly Dysregulated Expression in Calcium Homeostasis Pathway, Cerebellum. 16 (2017) 68–81. doi:10.1007/s12311-016-0762-4.

[106] D.A. Gold, S.H. Baek, N.J. Schork, D.W. Rose, D.D. Larsen, B.D. Sachs, et al., RORalpha coordinates reciprocal signaling in cerebellar development through sonic hedgehog and calcium-dependent pathways, Neuron. 40 (2003) 1119–1131.

[107] M.W. Vogel, M. Sinclair, D. Qiu, H. Fan, Purkinje cell fate in staggerer mutants: agenesis versus cell death, J. Neurobiol. 42 (2000) 323–337.

[108] C. Bettencourt, M. Ryten, P. Forabosco, S. Schorge, J. Hersheson, J. Hardy, et al., Insights from cerebellar transcriptomic analysis into the pathogenesis of ataxia, JAMA Neurol. 71 (2014) 831–839. doi:10.1001/jamaneurol.2014.756.

[109] M. Ingram, E.A.L. Wozniak, L. Duvick, R. Yang, P. Bergmann, R. Carson, et al., Cerebellar Transcriptome Profiles of ATXN1 Transgenic Mice Reveal SCA1 Disease Progression and Protection Pathways, Neuron. 89 (2016) 1194–1207. doi:10.1016/j.neuron.2016.02.011.

[110] H.T. Orr, M.-Y. Chung, S. Banfi, T.J. Kwiatkowski, A. Servadio, A.L. Beaudet, et al., Expansion of an unstable trinucleotide CAG repeat in spinocerebellar ataxia type 1, Nat. Genet. 4 (1993) 221–226. doi:10.1038/ng0793-221.

[111] S.M. Pulst, A. Nechiporuk, T. Nechiporuk, S. Gispert, X.-N. Chen, I. Lopes-Cendes, et al., Moderate expansion of a normally biallelic trinucleotide repeat in spinocerebellar ataxia type 2, Nat. Genet. 14 (1996) 269–276. doi:10.1038/ng1196-269.

[112] K. Sanpei, H. Takano, S. Igarashi, T. Sato, M. Oyake, H. Sasaki, et al., Identification of the spinocerebellar ataxia type 2 gene using a direct identification of repeat expansion and cloning technique, DIRECT, Nat. Genet. 14 (1996) 277–284. doi:10.1038/ng1196-277.

[113] Y. Kawaguchi, T. Okamoto, M. Taniwaki, M. Aizawa, M. Inoue, S. Katayama, et al., CAG expansions in a novel gene for Machado-Joseph disease at chromosome

14q32.1, Nat. Genet. 8 (1994) 221–228. doi:10.1038/ng1194-221.

[114] Y. Ikeda, K.A. Dick, M.R. Weatherspoon, D. Gincel, K.R. Armbrust, J.C. Dalton, et al., Spectrin mutations cause spinocerebellar ataxia type 5, Nat. Genet. 38 (2006) 184–190. doi:10.1038/ng1728.

[115] G. David, N. Abbas, G. Stevanin, A. Durr, G. Yvert, G. Cancel, et al., Cloning of the SCA7 gene reveals a highly unstable CAG repeat expansion, Nat. Genet. 17 (1997) 65–70. doi:10.1038/ng0997-65.

[116] M.D. Koob, M.L. Moseley, L.J. Schut, K.A. Benzow, T.D. Bird, J.W. Day, et al., An untranslated CTG expansion causes a novel form of spinocerebellar ataxia (SCA8), Nat. Genet. 21 (1999) 379–384. doi:10.1038/7710.

[117] T. Matsuura, T. Yamagata, D.L. Burgess, A. Rasmussen, R.P. Grewal, K. Watase, et al., Large expansion of the ATTCT pentanucleotide repeat in spinocerebellar ataxia type 10, Nat. Genet. 26 (2000) 191–194. doi:10.1038/79911.

[118] H. Houlden, J. Johnson, C. Gardner-Thorpe, T. Lashley, D. Hernandez, P. Worth, et al., Mutations in TTBK2, encoding a kinase implicated in tau phosphorylation, segregate with spinocerebellar ataxia type 11, Nat. Genet. 39 (2007) 1434–1436. doi:10.1038/ng.2007.43.

[119] S.E. Holmes, E.E. O'Hearn, M.G. McInnis, D.A. Gorelick-Feldman, J.J. Kleiderlein, C. Callahan, et al., Expansion of a novel CAG trinucleotide repeat in the 5' region of PPP2R2B is associated with SCA12, Nat. Genet. 23 (1999) 391–392. doi:10.1038/70493.

[120] D.-H. Chen, Z. Brkanac, C.L.M.J. Verlinde, X.-J. Tan, L. Bylenok, D. Nochlin, et al., Missense mutations in the regulatory domain of PKC gamma: a new mechanism for dominant nonepisodic cerebellar ataxia, Am. J. Hum. Genet. 72 (2003) 839–849.

[121] K. Nakamura, S.Y. Jeong, T. Uchihara, M. Anno, K. Nagashima, T. Nagashima, et al., SCA17, a novel autosomal dominant cerebellar ataxia caused by an expanded polyglutamine in TATA-binding protein, Hum. Mol. Genet. 10 (2001) 1441–1448.

[122] M.A. Knight, D. Hernandez, S.J. Diede, H.G. Dauwerse, I. Rafferty, J. van de Leemput, et al., A duplication at chromosome 11q12.2-11q12.3 is associated with spinocerebellar ataxia type 20, Hum. Mol. Genet. 17 (2008) 3847–3853. doi:10.1093/hmg/ddn283.

[123] J. Delplanque, D. Devos, V. Huin, A. Genet, O. Sand, C. Moreau, et al., TMEM240 mutations cause spinocerebellar ataxia 21 with mental retardation and severe cognitive impairment, Brain. 137 (2014) 2657–2663. doi:10.1093/brain/awu202.

[124] K.E. Hekman, G.-Y. Yu, C.D. Brown, H. Zhu, X. Du, K. Gervin, et al., A conserved eEF2 coding variant in SCA26 leads to loss of translational fidelity and increased susceptibility to proteostatic insult, Hum. Mol. Genet. 21 (2012) 5472–5483. doi:10.1093/hmg/dds392.

[125] J.C. van Swieten, E. Brusse, B.M. de Graaf, E. Krieger, R. van de Graaf, I. de Koning, et al., A Mutation in the Fibroblast Growth Factor 14 Gene Is Associated with

Autosomal Dominant Cerebral Ataxia, The American Journal of Human Genetics. 72 (2003) 191–199. doi:10.1086/345488.

[126] N. Sato, T. Amino, K. Kobayashi, S. Asakawa, T. Ishiguro, T. Tsunemi, et al., Spinocerebellar ataxia type 31 is associated with "inserted" penta-nucleotide repeats containing (TGGAA)n, Am. J. Hum. Genet. 85 (2009) 544–557. doi:10.1016/j.ajhg.2009.09.019.

[127] M. Cadieux-Dion, M. Turcotte-Gauthier, A. Noreau, C. Martin, C. Meloche, M. Gravel, et al., Expanding the clinical phenotype associated with ELOVL4 mutation: study of a large French-Canadian family with autosomal dominant spinocerebellar ataxia and erythrokeratodermia, JAMA Neurol. 71 (2014) 470–475. doi:10.1001/jamaneurol.2013.6337.

[128] J.-L. Wang, X. Yang, K. Xia, Z.M. Hu, L. Weng, X. Jin, et al., TGM6 identified as a novel causative gene of spinocerebellar ataxias using exome sequencing, Brain. 133 (2010) 3510–3518. doi:10.1093/brain/awq323.

[129] H. Tsoi, A.C.S. Yu, Z.S. Chen, N.K.N. Ng, A.Y.Y. Chan, L.Y.P. Yuen, et al., A novel missense mutation in CCDC88C activates the JNK pathway and causes a dominant form of spinocerebellar ataxia, J. Med. Genet. 51 (2014) 590–595. doi:10.1136/jmedgenet-2014-102333.

[130] C. Depondt, S. Donatello, M. Rai, F.C. Wang, M. Manto, N. Simonis, et al., MME mutation in dominant spinocerebellar ataxia with neuropathy (SCA43), Neurol Genet. 2 (2016) e94. doi:10.1212/NXG.0000000000000094.

[131] L.M. Watson, E. Bamber, R.P. Schnekenberg, J. Williams, C. Bettencourt, S. Jayawant, et al., Dominant Mutations in GRM1 Cause Spinocerebellar Ataxia Type 44, Am. J. Hum. Genet. 101 (2017) 638. doi:10.1016/j.ajhg.2017.09.006.

Figure legends

Figure 1: Gene sharing within cerebellar cell types. Venn diagram of gene sharing between six cerebellar cell types including Purkinje Cells, cerebellar granule cells, cerebellar golgi cells, cerebellar oligos (mature oligodendrocytes; Cmtm5), cerebellar oligos (mixed population of mature and progenitor oligodendrocytes;Olig2), and cerebellar astrocytes. Numbers in parentheses are the total number of genes found for that cell type; numbers in intersections show the total number of genes shared between given combinations of cerebellar cell types.

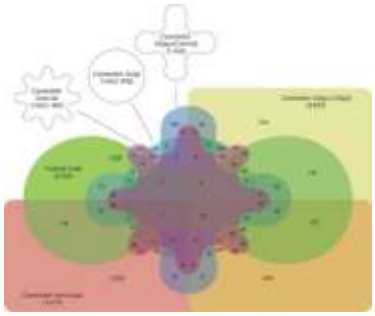

Table 1: List of known SCA genes and mutations

SCA type	Gene name	OMIM number	Locus	Mutation type	Protein name	Reference
SCA1	*ATXN1*	164400	6p22.3	(polyQ)n	Ataxin-1	[110]
SCA2	*ATXN2*	183090	12q24.12	(polyQ)n	Ataxin-2	[111,112]
SCA3	*ATXN3*	607047	14q32.12	(polyQ)n	Ataxin-3	[113]
SCA5	*SPTBN2*	600224	11q13.2	Deletion, MM	Spectrin beta chain, non-erythrocytic 2	[114]
SCA6	*CACNA1A*	183086	19p13.13	(polyQ)n	Voltage-dependent P/Q-type calcium channel subunit alpha-1A	[21]
SCA7	*ATXN7*	164500	3p14.1	(polyQ)n	Ataxin-7	[115]
SCA8	*KLHL1AS*	608768	13q21	(CTG/CAG)n[a]	Ataxin-8	[116]

SCA10	*ATXN10*	603516	22q13.31	(ATTCT)n [a]	Ataxin-10	[117]
SCA11	*TTBK2*	604432	15q15.2	Frameshift/ deletion	Tau-tubulin kinase 2	[118]
SCA12	*PPP2R2B*	604326	5q32	(CAG)n [a]	Serine/threonine-protein phosphatase 2A 55 kDa regulatory subunit B beta isoform	[119]
SCA13	*KCNC3*	605259	19q13.33	MM	Potassium voltage-gated channel subfamily C member 3	[23]
SCA14	*PRKCG*	605361	19q13.42	MM	Protein kinase C gamma type	[120]
SCA15/ 16/29	*ITPR1*	606658	3p26.1	Deletion	Inositol 1,4,5-trisphosphate receptor type 1	[24-26]

SCA17	*TBP*	607136	6q27	(polyQ)n	TATA-box-binding protein	[121]
SCA19/22	*KCND3*	607346	1p13.2	MM/deletion	Potassium voltage-gated channel subfamily D member 3	[5,6]
SCA20	*DAGLA*	608687	11q12	12 gene duplication	Sn1-specific diacylglycerol lipase alpha	[122]
SCA21	*TMEM240*	607454	1p36.33	MM	Transmembrane protein 240	[123]
SCA23	*PDYN*	610245	20p13-p12.2	MM/frameshift	Proenkephalin-B	[8]
SCA26	*eEF2*	609306	19p13.3	MM	Elongation factor 2	[124]
SCA27	*FGF14*	609307	13q33.1	MM	Fibroblast growth factor 14	[125]
SCA28	*AFG3L2*	610246	18p11.21	MM	AFG3-like protein 2	[27]
SCA31	*BEAN*	117210	16q21	(TGGAA)n [a]	Protein BEAN1	[126]

SCA34	*ELOVL4*	133190	6q14.1	MM	Elongation of very long chain fatty acids protein 4	[127]
SCA35	*TGM6*	613908	20p13	MM	Protein-glutamine gamma-glutamyltransferase 6	[128]
SCA36	*NOP56*	614153	20p13	(GGCCTG)n [a]	Nucleolar protein 56	[3]
SCA37	*DAB1*	615945	1p32.2	(ATTTC)n [a]	Disabled homolog 1	[4]
SCA38	*ELOVL5*	615957	6p12.1	MM	Elongation of very long chain fatty acids protein 5	[93]
SCA40	*CCDC88C*	616053	14q32.11-q32.12	MM	Protein Daple	[129]
SCA41	*TRPC3*	616410	4q27	MM	Short transient receptor potential channel 3	[7]

SCA42	*CACNA1G*	616795	17q21.33	MM	Voltage-dependent T-type calcium channel subunit alpha-1G	[22]
SCA43	*MME*	617018	3q25.2	MM	Neprilysin	[130]
SCA44	*GRM1*	617691	6q24.3	MM	Metabotropic glutamate receptor 1	[131]
Unknown	*FAT2*	604269	5q33.1	MM	Protocadherin Fat 2	[94]
Unknown	*PLD3*	615698	19q13.2	MM	Phospholipase D3	[94]
Unknown	*KIF26B*	614026	1q44	MM	Kinesin-like protein KIF26B	[94]
Unknown	*EP300*	602700	22q13.2	MM/frameshift	Histone acetyltransferase p300	[94]
Unknown	*FAT1*	600976	4q35.2	MM	Protocadherin Fat 1	[94]

MM = missense mutations, polyQ = polyglutamine , [a] = noncoding, and (…)n = repeat expansions

Table 2: List of Purkinje cell pathways

Pathway	Source	Gene symbols	p-value
Phosphatidylinositol signaling	KEGG	*DGKZ; INPP5A; PLCB3; INPP5D; INPP5E; PRKCA; CDS1; PIP5K1A; INPP4A; ITPKA; IMPA1; DGKH; PI4K2A; MTMR7; ITPR1; DGKG*	3.20×10^{-8}
Huntington's disease	KEGG	*NDUFA6; NDUFC1; NDUFA4; PLCB3; NDUFA2; GNAQ; SOD1; TGM2; CYCS; CASP9; GPX1; COX6C; PPIF; POLR2L; ITPR1; ATP5G1; AP2B1; POLR2K*	1.79×10^{-5}
MAPK signaling	KEGG	*RELA; TGFB1; TGFB2; RPS6KA3; PTPRR; PPM1A; NLK; MKNK1; CACNB2; FGF11; RAP1B; DUSP10; MEF2C; PRKCA; MAP4K2; FGF7; CACNG2; CACNA1G; MAPKAPK2; TNF; PPM1B*	2.44×10^{-5}
Inositol phosphate metabolism	KEGG	*INPP5A; PLCB3; INPP5D; INPP5E; PIP5K1A; INPP4A; ITPKA; IMPA1; PI4K2A; MTMR7*	4.37×10^{-5}
Nuclear Receptors	Wikipathways	*ESRRA; ESRRB; NR2F6; RORA; NR2F2; NR2C2; PGR*	1.10×10^{-4}
p38 mapk signaling pathway	BioCarta	*NR2C2; MAP3K9; MKNK1; MEF2C; MEF2D; MAPKAPK2*	3.11×10^{-3}